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10/646,454	08/21/2003	William F. Kiesman	A085 CON	9532

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/646,454	KIESMAN ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 39-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The "R_5-alkylamino" substituent of choice (a) and (b) is ambiguous. The R_5 could be on the alkyl, or it could be the second substituent on the N. Whichever choice is selected, applicants must demonstrate that the specification makes clear that this choice, not the other, was intended.
2. The same problem occurs with the heterocyclylalkylamino on e.g. page 6, line 8. Is this (heterocyclyl)(alkyl)amino or (heterocyclylalkyl)amino.
3. Claim 2 is improperly dependent on claim 1. Claim 1 has no provision for salts.
4. The term "acyl" is indefinite. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R? For example, at page 91, line 44, an sulfoxy group is attached to what?
5. "Substituted" --- with what? (e.g. page 90, line 13).

6. The last two choices on 4th line of the R5 definition appear to be misdrawn. It appears to provide $S(O)_2$-O-N~, which as a sulfonated hydroxylamine would be expected to be too reactive in a pharmaceutical. Is this what is intended?

7. The Phrase "condition characterized by" is ambiguous. It could refer to a condition which has this as its cause, or a condition which has this as its effect.

8. The term "elevated adenosine concentration" is ambiguous. Concentration measured how and where? Elevated as compared to what? Zero? The lowest normal level? The highest "normal" level? The average level? What is the "normal" range/average? Terms of degree are indefinite when the specification contains no "explicit guidelines" to distinguish from things which are not so, *Ex parte Oetiker*, 23 USPQ2d 1651, 1655 (1990). See also *Ex Parte Anderson*, 21 USPQ2d 1241 at 1250. Thus, there is no way of knowing what claim 40 covers.

9. Similar issues apply to "increased sensitivity to adenosine." Increased as compared to what? What tests are to be used to measure sensitivity? What if one test shows increased, another does not? Does the increase have to be statistically significant?

10. The claim 41 disorder "hyperactivity" is vague: Hyperactivity of what? Almost anything in the body can be hyperactive. This would cover too much activity from any gland, e.g. adrenal gland; any system e.g. immune system; any muscle, e.g. heart. It is impossible to know what is actually intended here.

11. Choices 3, and 8-10 are poorly drawn on page 4. The examiner assumer that the bridge on the right is intended as a three carbon bridge, but the "angle" for one of the carbons is so slight that this may well be printed incorrectly. A more clear structure is required.

Claims 1-6, 11, 39-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. The replacement of "phosphate" with phosphono (i.e. $-P(O)(OH)_2$) is new matter. Applicants have presented no evidence that one of ordinary skill in the art could have figured out that this group, as opposed to the e.g. dimethylphosphate or "phosphine" etc was intended. Indeed, in the parent, applicants stated (paper of 7/25/2002, page 5) that what was intended was the $-OP(O)(OH)_2$ group. It is not seen how applicants can assert that surely the phosphono group was intended when they themselves has already said that the $-OP(O)(OH)_2$ group was actually intended.

The replacement of carbonyl with oxo is not new matter. This is seen in the 11th (not the 13th) compound in Figure IB.

Claims 40-42 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some disorders, does not reasonably provide enablement for cardiac and circulatory disorders, degenerative disorders of the central nervous system, Parkinson's disease, post-stroke neurological deficit, dyslexia, hyperactivity, cystic fibrosis, edematous conditions, renal dysfunction, and the generic language of claim 40. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the very broad scope of R3 (including the deeply nested nature of the substituents), R1 and R2 and R6, trillions of compounds are covered.

(b) Scope of the diseases covered. A few are individual diseases, but most are broad categories. For example:

I. Cardiac and circulatory disorders embraces a vast array of problems, some of which are contradictory to others. This covers various forms of endocarditis, including Verrucous, Atypical verrucous (Libman-Sacks) Non-bacterial thrombotic - NBTE (marantic), bacterial, viral, and rickettsial endocarditis. It covers different forms of atresia, including tricuspid atresia without TGV, pulmonic valvular atresia and aortic atresia. It includes assorted cardiomyopathies, including restrictive cardiomyopathy,

peripartum cardiomyopathy, hypertrophic cardiomyopathy, and congenital cardiomyopathy. It embraces various forms of aortic Stenosis, including valvular aortic Stenosis, idiopathic hypertrophic sub-aortic stenosis (IHSS), subvalvular aortic stenosis, and supravalvular aortic stenosis. There are all kinds of miscellaneous syndromes, including subclavian steal syndrome, Eisenmenger syndrome, mitral valve prolapse (Barlow) syndrome, Aortic arch syndrome, scimitar syndrome, hypoplastic left heart syndrome, Lutembacher syndrome, and superior vena cava syndrome. It covers various forms of hypertension, including primary (idiopathic) pulmonary hypertension, neonatal pulmonary venous hypertension and pulmonary hypertension. It includes aortic aneurysms, including both thoracic and abdominal, as well as mycotic aneurysm. It covers various types of arrhythmias and atrial fibrillation. It covers elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, and hyperlipoproteinaemias. It covers different forms of ischaemic heart disease including congestive heart failure and myocardial infarction. It covers a vast array of structural defects such as atrial septal defect (ASD), aorticopulmonary window, egg-on-its-side heart, gooseneck deformity, endocardial cushion defect, arc of Buehler, arc of Riolan, truncus arteriosus, Ebstein's Malformation, azygos continuation of interrupted IVC, Atrioventricular Canal, ventricular septal defect (VSD), abdominal aortic coarctation, aortic pseudo-coarctation, complete endocardial cushion defect, Hypoplastic Left Heart, patent ductus arteriosus (PDA), congenital absence of pulmonary valve, aortic coarctation partial endocardial cushion defect, Single Ventricle, box-like heart, pulmonary sling, Left Ventricle to Right Atrial Shunt, total anomalous pulmonary venous return (TAPVR), partial anomalous pulmonary venous return (PAPVR), and transposition of the great vessels. It covers

certain peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis and assorted cerebral vascular diseases including migraine. There is hypotension, which can arise from all sorts of other problems. There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obliterans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilicalis, and verminous mesenteric arteritis. There are differet forms of Vascular dementia, including multi-infarct dementia (MID), Binswanger's Disease and Arteriosclerotic Dementia. There is a huge collection of other cardiovascular problems, including thymoma (invasive and non-invasive), admixture lesion, left ventricular hypertrophy, tortuous aorta, aortic laceration pulmonary artery sarcoma, aortic regurgitation, pneumomediastinum (Spontaneous and traumatic), middle mediastinal mass, posterior mediastinal mass, Uhl disease, right ventricular hypertrophy, cardiac rhabdomyoma,

acute aortic dissection, pericardial cyst, carotid artery bruit, pulmonary embolism, venous angioma, varicose veins and spider veins, congenital heart disease, pericardial effusion, tetralogy of Fallot, coronary artery calcification, endocardial fibroelastosis, fibromuscular dysplasia (FMD), thromboangiitis obliterans (Buerger disease), left or right ventricular volume overload, situs inversus, neonatal heart failure, myocarditis, arteriosclerosis, atherosclerosis, stroke and many others.

II. Neurodegenerative disorders covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; the vascular dementias (which are usually caused by cerebral infarction and include multi-infarct dementia (MID), strategic infarct dementia, LID, ThD, and Binswanger's disease); Lewy Body dementia; Senile dementia of the neurofibrillary tangle type ("tangle-only dementia"); Gerstmann-Straussler-Scheinker Disease (GSS); Pick's disease, dementia of the frontal lobe type (DFT) and DFT with motor neuron disease (DFT-MND); Hallervordon-Spatz disease; progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Senile dementia of the neurofibrillary tangle type ("tangle-only dementia"); Lafora disease, cortical-basal ganglionic degeneration (CBGD); Ramsay Hunt Syndrome Type II; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal

muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); ophthalmic disorders such as primary open-angle glaucoma (POAG) and retinitis pigmentosa; Leber's Disease; Alper's disease; Wallerian degeneration, and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give no dementia and affect only vision, such as POAG. Some give progressive dementia without other prominent neurological signs, such as Alzheimer's Disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give seizures and myoclonus, e.g. Lafora disease and Alper's disease, but most do not. Lewy Body Dementia gives a combination of parkinsonian effects, fluctuating cognition and visual hallucinations not seen in other neurodegenerative disorders. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some cause deafness e.g. Alper's disease, which is believed to be a metabolic disorder. Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's Disease and FTDP-17, and other such as Parkinson's clearly do not. Lafora disease (which is a hereditary) is characterized by the presence of inclusion bodies, known as Lafora bodies, within the cells of neurons. Alper's disease causes status spongiosus of the cerebral grey matter. Some affect only vision such as retinitis pigmentosa, while others affect both vision and cognitive functions, such as Posterior cortical atrophy (PCA). Even within those that fall into the same category of effects,

there are often striking differences. For example, Alzheimer's Disease and Pick's disease both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's Disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's Disease. Some normally strike young children (e.g. Alper's disease also known as progressive infantile poliodystrophy), some in adolescence (e.g. Lafora disease), some are primarily seen in middle age (most forms of frontotemporal dementia strike in the 40s or 50s), others are seen almost entirely in the aged e.g. Binswanger's disease, and some have no age distribution at all (e.g. CJD).

III. Hyperactivity, as noted above, could be excess activity of any organ whatsoever in the body, any metabolic path, any receptor, any cell type, any enzyme, etc.

IV. Renal dysfunction is any dysfunction at all of the kidneys. There are scores and scores of kidney diseases, all of which cause dysfunction, and these are extremely diverse in nature and origin. There are an assortment of tropical bacterial nephropathies, arising from Salmonellosis, typus, Leprosy, Leptospirosis and others. There is also membranoproliferative glomerulonephritis caused by Hepatitis C, and membranous glomerulonephritis caused by Hepatitis B. There are numerous forms of vasculitis which affect the kidney, such as Polyarteritis nodosa (PAN), Takayasu's disease (Pulseless disease), Kawasaki disease, Temporal arteritis (Giant cell arteritis), Churg-Strauss syndrome, Microscopic Polyarteritis (MPA), Wegener's granulomatosis, Henoch –Schonlein Purpura, Goodpasture's syndrome, Micrtoscopic polyanglitis, Cryoglobulinemic vasculitis, Lupus vasculitis and others. There are various forms of

Amyloidosis: Primary amyloidosis (AL), Secondary amyloidosis (AA), Familial amyloidosis (AF), Senile systemic amyloidosis (AS), and Dialysis amyloidosis (AD). There are an assortment of Acid-Base Disorders including or arising from Alcoholic Ketoacidosis, Chronic Renal Failure, Diabetic Ketoacidosis, Cyanide Poisoning, Glycol Abuse, Lactic Acidosis, Metabolic Acidosis, Metabolic Alkalosis, Methanol Abuse, Respiratory Acidosis, Respiratory Alkalosis and Salicylate Poisoning. There are Fluid and Electrolyte Disturbances i.e. in Calcium, Magnesium, Phosphate, Potassium, Sodium as well as Water Imbalance. There is a heterogeneous collection of polycystic kidney diseases, which are autosomal, and have been linked to three different genes. It includes numerous renal tube disorders, including Fanconi's syndrome, hartnup disease, Renal glucosuria, the entire family of Bartter syndromes, Dent's disease, Blue diaper syndrome and many more. There is also nephroblastema, nephroblastoma, nephroblastomatosis, nephrocalcinosis, nephrocele, nephrogenic adenoma, nephrogenic diabetes insipidus, nephromalacia, mesoblastic nephroma, nephromegaly, nephroptosis, nephrosclerosis, nephrotic oedema, renal multicycstic dysplasia, and nephrotuberculosis. There are various forms of diabetic nephropathy and there is sickle cell disease. There are also an assortment of hereditary and congenital glomerular disorders, including Alport's syndrome, benign familiar hematuria, Fabry's disease, nail-patella syndrome, Lecithin-chlolesterol acyl transferase deficiency (an autosomal recessive disorder), Lipoprotein glomerulopathy, nephropathic cystinosis, congenital nephritic syndrome of the Finnish type, and diffuse mesangial sclerosis.

V. Edematous conditions covers any form of swelling arising from any condition. Swelling can occur in any soft tissue. It can arise from almost any type of inflammation or failure of the body's system for balancing fluids.

VI. Claim 40 scope as noted above is simply unknown.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information appears to be completely absent.

(4) State of the Prior Art: So far as the examiner is aware, no compounds of any kind have been used for the treatment of anything even remotely similar to such a scope.

(5) Working Examples: There are no working examples to the treatment of any disorder.

(6) Skill of those in the art: The skill level in these area tends to be varied but is often low or extremely low. Some examples:

A. The skill level in the art of pharmacological treatment of cardiovascular disorders varies with the disorder. In some areas such as hypertension it is relatively high. But in the great majority of cases it is very low as the disorders cannot be treated with pharmaceuticals. There are a wide variety of causes. For example, just for the Vascular dementias, these can be caused when caused when small arteries in the brain burst (cerebral hemorrhage), or arteries are blocked by plaque formation or clots (thrombosis

or embolism), or there is insufficient blood flow to parts of the brain (ischemia). Stroke is the most common cause, but it can arise from auto-immune inflammatory diseases of the arteries such as Systemic Lupus Erythermotsis and Temporal Arteritis; sometimes the cause is completely unknown. A huge assortment of inflammatory processes can result in various forms of vasculitis. Genetic defects and developmental problems are responsible for many types of structural problems. Metabolic disorders such as Mucopolysaccharidosis I (the cause of Hurler- Scheie syndrome) can cause vascular deposits of mucopolysaccharides with arteriosclerosis, heart murmur, and aortic regurgitation. The vast majority are treated either by surgical means or cannot be treated at all, leaving only general management of symptoms.

B. Treatment of renal dysfunction varies considerably; many cannot be treated pharmaceutically but require either dialysis or surgery. Many have no treatment of any kind.

C. The great diversity of diseases falling within the neurodegenerative disorder category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. The vast majority have no treatment at all and many of them are very difficult to even get a clear diagnosis on. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's Disease has produced are almost entirely means of providing Acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.

D. The skill level for Parkinson's Disease is very low relative to the difficulty of task. Parkinson's Disease is a neurodegenerative disorder which, like most neurodegenerative disorders, has been highly resistant to pharmaceutical treatment. The disorder is characterized by a deficiency of dopamine. This deficiency arises from the degeneration of dopamine-producing cells in the substantia nigra, located in the midbrain, along with the presence of cytoplasmic protein inclusions called Lewy bodies. PD is considered to be a cluster of related disorders. The majority of cases of PD are deemed sporadic, but there are also familial forms of PD. The degeneration is of unknown origin (idiopathic), and cannot itself be stopped. Current drug regimens for Parkinson's disease are aimed instead at symptomatic relief, primarily through a dopaminergic effect. This includes dopamine replacement therapy (L-dopa), COMT inhibitors (which facilitate the conversion of L-Dopa to dopamine itself), Amantadine (which appears to increase dopamine synthesis), dopamine agonists (which mimic dopamine) or MAO B inhibitors (e.g. Selegeline which reduces or delays the breakdown of dopamine), but these do not actually treat the disease itself. At the time of filing, and indeed at present, no drug has been scientifically demonstrated to treat the disease itself, rather than provide relief for this or that symptom. For example, L-dopa does not treat the underlying problem of cell death. Indeed, the medications used to treat the symptoms of Parkinson's disease cannot stop the disease from progressing over time.

E. Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these

problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics and antithrombotics don't get at the neurological damage caused, but are mostly done to insure adequate cardiac functioning. Thus, effective acute drug treatment of the neurological damage cause by the stroke has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well. While it is true that adenosine modulators have also been tried, this is just one of many unsuccessful approaches. Further, as best

the examiner understands this, this research has been done with agents such as vinpocetine, to stimulate adenosine, which appears to be the opposite of what these agents do. Clearly, accomplishing such a goal involves more than routine experimentation.

F. Dyslexia and related disorders such as dyscalculia have been so far completely resistant to any pharmaceutical treatment, in part because the neurological basis of it has not been determined.

G. Cystic Fibrosis has no pharmaceutical treatment per se. Drugs used for this are just supportive, for relief of symptoms.

H. The claim 40 language, Hyperactivity and edematous conditions are vast arrays of disorders which cannot be treated generally.

(7) The quantity of experimentation needed: In view of the above, especially factors 1, 3, 5 and 6, the level of experimentation required is expected to be quite great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 11, 39-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and others of U.S. Patent No. 6649600. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is extensive overlap with the claims of the parent. For example, if R3 is option a) and is unsubstituted, then there is overlap (even with claim 11). Also, note that in the b) list of substituents for option a), applicants have retained the R5-alkylsulfonyl and R5-alkylthio, but these were in the parent patent as well.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpat99entable over Suzuki '782, WO 94/16702, Suzuki et al (1992), or Shimada et al (1992).

In Suzuki '782, see examples 29 (no linker) and 11 (methylene linker). In WO 04/16702, see compound G and E. In Shimada et al (1992), see 44 and 45. In Suzuki et al (1992), see 22 and 23. These show the adamantyl compound, with or without methylene linker. Applicants have the same, except that the adamantyl has a methyl group stuck on. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific theaching to add or remove methyl groups. See *In re Wood,* 199 USPQ 137; *In re Hoke,* 195 USPQ 148; *In re Lohr,* 137 USPQ 548; *In re Magerlein,* 202 USPQ 473; *In re Wiechert,* 152 USPQ 249; *Ex parte Henkel,* 130 USPQ 474; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque,* 121 USPQ 425; *In re Druey,*

138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. See also MPEP 2144.09, second paragraph.

Further, the feature of a methyl group attached to the 8-position substituent is seen in example 5 of Suzuki '782.

Note that in the parent, this rejection was overcome by the removal of the tricyclic group option, but this has been retained in the instant claim 1.

Specification

The abstract is objected to as incomplete. The essence of the invention is in R3, which is not defined. Suggested is the abstract used in the parent.

The specification is objected to as having numerous typographical errors. These were noted in the Certificate of correction as presented in the parent; these need to be fixed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571)272-0674. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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11/29/04